Brief Communication

Learning in the absence of experience-dependent regulation of NMDAR composition

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Olfactory discrimination (OD) learning consists of two phases: an initial *N*-methyl-D-aspartate (NMDA) receptor-sensitive rule-learning phase, followed by an NMDA receptor (NMDAR)-insensitive pair-learning phase. The rule-learning phase is accompanied by changes in the composition and function of NMDARs at synapses in the piriform cortex, resulting in a high level of the NR2a subunit relative to NR2b. Here we show that the learning-induced changes in NMDAR composition in the adult piriform cortex are due to a decrease in the level of the NR2b subunit protein, rather than an increase in the level of NR2a. Chronic administration of an NMDAR open channel blocker during training delays OD learning and blocks learning-induced changes in NMDAR subunit composition. However, the animals still learn the OD task. Our data demonstrate that learning can occur in the absence of activity-dependent regulation of NMDAR composition, suggesting differences in the mechanism for long-term maintenance of NMDAR-dependent and NMDAR-independent learning.

The dual activation requirement of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor (NMDAR) is thought to enable the induction of many types of activity-dependent synaptic modifications, such as long-term potentiation (LTP) (Bliss and Collingridge 1993), long-term depression (LTD) (Bear and Abraham 1996), sensory system maturation (Carmignoto and Vicini 1992; Quinlan et al. 1999a), and learning (Morris et al. 1986; Tsien et al. 1996; Tang et al. 1999). However, increasing evidence suggests that NMDAR-dependent and NMDAR-independent forms of synaptic plasticity coexist, each with a distinct time course, pharmacological sensitivity, and downstream molecular components. For example, intraventricular infusion of an NMDAR antagonist prior to training in the water maze impairs spatial learning but does not impair visual learning (Morris et al. 1986). However, learning in the water maze becomes NMDAR independent if subjects are pre-trained in another maze (Bannerman et al. 1995) or in a nonspatial task (Saucier and Cain 1995). Similarly, different phases of learning a complex task may recruit different mechanisms of synaptic plasticity. The early phase of the extinction of conditioned fear is insensitive to inhibition by NMDAR antagonists, whereas the later consolidation phase is NMDAR dependent (Santini et al. 2001). Differential sensitivity to NMDAR antagonism has also been demonstrated in the two phases of olfactory-discrimination (OD) learning. The initial rule-learning phase is significantly delayed in the presence of the NMDAR open channel blocker MK801; however, once the subjects become familiar with the task, MK801 has no effect on subsequent OD learning (Quinlan et al. 2004). The initial NMDAR-dependent phase of OD learning is also accompanied by a change in the composition and function of NMDARs at synapses in the piriform cortex and a subsequent change in the characteristics of NMDAR-dependent synaptic plasticity (Lebel et al. 2001).

NMDAR composition is a primary determinant of NMDAR function. NMDARs are heteromeric protein complexes composed of NR1, NR2, and NR3 subunit proteins (Monyer et al. 1994).

Multiple isoforms of the NR2 subunit (NR2a–NR2d) exist, each of which confers to NMDARs distinct pharmacological sensitivity, biophysical properties, and links to intracellular signaling cascades. In the neonatal mammalian cortex, functional NMDARs contain NR1 and NR2b, and produce excitatory postsynaptic currents (EPSCs) that are relatively long in duration. Over the course of postnatal development, these are replaced or supplemented by NMDARs containing NR2a, resulting in a shortening of NMDAR EPSCs (Carmignoto and Vicini, 1992; Quinlan et al. 1999b; Roberts and Ramoa 1999). Visual deprivation, by dark-rearing from birth, attenuates the developmental increase in NR2a/NR2b, while bringing a dark-reared animal out into the light rapidly induces NMDAR maturation. The rapid, experience-dependent increase in NR2a is blocked by the NMDAR antagonist APV (Quinlan et al. 1999b), demonstrating that in the neonatal visual cortex, the regulation of NMDAR composition and function is dependent on NMDAR activation.

We have recently shown that NMDAR subunit composition in the adult cortex is regulated by learning. OD learning in adults induced an increase in NR2a/NR2b in synaptoneurosomes prepared from the piriform (olfactory) cortex (Quinlan et al. 2004). A decrease in the duration of the pharmacologically isolated NMDAR-dependent fEPSPs and an increase in the threshold for long-term potentiation accompanied this change in NMDAR subunit composition. Here we explore the nature of the learning-induced NMDAR subunit switch and ask whether the learning-induced regulation of NMDARs is dependent on NMDAR activation.

Results

Adult male, Sprague-Dawley rats were maintained on a 23.5-h water-deprivation schedule, with food available ad libitum, for 3 d before the beginning of olfactory discrimination training in a 4-arm radial maze (Fig. 1A). At the beginning of each session, an electronic signal randomly opens two valves, releasing a positive cue odor into one arm and a negative cue odor into the other. During training, if the animal enters the arm containing the positive cue odor, a drop of drinking water is released into the well at the end of that arm. The association between water reward and odor is random for pseudo-trained controls. An age-matched group of naive controls was water-deprived, but not exposed to

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Figure 1. Olfactory discrimination (OD) learning is delayed but not prevented by NMDAR channel blockers. (A) Schematic of the four-arm maze. Protocols for trained and pseudo-trained rats were similar: An electronic start command randomly opens two of the eight valves, releasing pressured air streams with a positive-cue odor into one arm and negative-cue odor into another. After eight seconds, the doors allowing access to the two selected arms are opened to allow entrance. When the animal reaches the end of an arm (90 cm from start), an infrared beam is interrupted (arrowhead) and a drop of drinking water (W) is released into the drinking well. For the trained group, water is delivered only if the arm contains the positive-cue odor. For the pseudo-trained group, water and odors are randomly associated. A trial ends when the subject interrupts an infrared beam, or 10 sec after the start. A fan is operated for 15 sec between trials to remove odors. (B) Daily pre-training injections of the NMDAR open channel blocker MK801 delays, but does not prevent, OD learning. In control, saline-treated subjects, the average time to reach criterion for learning to discriminate between the first pair of odors, defined as $\geq 80\%$ correct responses in the last 10 trials of the day, is 6.12 ± 0.48 d (average $\pm$ SEM, $n = 8$; open symbols). Daily injection of the NMDAR channel blocker MK801 (0.1 mg/kg intraperitoneally) prior to each training session significantly delayed the time to reach criterion for learning the task (average $\pm$ SEM = 8.90 ± 0.23 d, $n = 8$, closed symbols, $P = 0.001$, t -test). Differences in task performance in MK801-treated subjects were seen at days 6–8 of training ($*P \leq 0.05$, t -test, versus saline controls). (C) Differential regulation of NMDAR composition by NMDAR-dependent and NMDAR-independent learning. When OD learning is achieved in the absence of MK801 (saline controls), we see a significant increase in the level of NR2a/NR2b in trained animals versus naive and pseudo-trained controls. However, when OD learning is achieved in the presence of pre-training injection of MK801, we see no change in the level NR2a/NR2b (one-way ANOVA, $F_{(5,40)} = 4.141$, $P < 0.01$, $*P < 0.02$ vs. naive saline in post hoc comparisons). Values are normalized to the average naive saline run on the same gel.

odors, rewards, or the maze. The average time to reach criterion for learning to discriminate between the first pair of odors, defined as $\geq 80\%$ correct responses in the last 10 trials of the day, is 6.12 ± 0.48 d ($n = 8$; open symbols, Fig. 1B). A daily injection of the NMDAR open channel blocker MK801 (0.1 mg/kg intraperitoneally) prior to each training session induced a significant increase in the time to reach criterion for learning (8.90 ± 0.23 d, $n = 8$, closed symbols, MK801, $n = 8$, $P = 0.001$, t -test). The performance of the MK801-treated subjects did not differ from chance (50% correct choices) on days 6–8 of training (all $P > 0.05$; t -test versus chance). A higher dose of MK801 (0.2 mg/kg intraperitoneally) further delayed, but did not inhibit, OD learning (time to reach learning criterion: 12.8 ± 4.2 d, $n = 8$; not shown).

We used quantitative immunoblotting of synaptoneurosomes prepared from the piriform cortex to examine changes in NMDAR subunit composition when OD learning was achieved in the absence or presence of MK801. As expected, when training

occurs in the absence of MK801, we see a significant increase in NR2a/NR2b (% of naive controls: pseudo-trained: $111.2 \pm 5.3\%$, $n = 7$; trained: $125.5 \pm 11.1\%$, $n = 8$). However, when OD learning is achieved in the presence of pre-training injections of MK801 (0.1 mg/kg, intraperitoneally), we see no significant difference in the level NR2a/NR2b (% of naive saline controls: naive MK801: $95.5 \pm 8.4\%$, $n = 8$; pseudo-trained MK801: $83.6 \pm 4.2\%$, $n = 8$; trained MK801: $92.8 \pm 7.0\%$, $n = 8$; one-way ANOVA $F_{(5,40)} = 4.141$, $P < 0.01$, $*P < 0.02$ vs. naive saline controls in post hoc comparisons; Fig. 1C). This suggests that NMDAR-independent learning does not regulate NMDAR subunit composition.

The learning-induced increase in NR2a/NR2b may be due to (1) an increase in the level of NR2a or (2) a decrease in the level of NR2b or (3) both. To distinguish between these possibilities, we analyzed independently the levels of each of the NR2 subunit proteins that predominate in the postnatal rodent cortex. Surprisingly, quantitative immunoblotting of synaptoneurosomes did not reveal a significant difference in the level of NR2a following OD learning either in the absence (% of naive saline controls: pseudo-trained: $102.0 \pm 17.3\%$, $n = 7$; trained: $94.3 \pm 6.7\%$, $n = 8$) or presence of MK801 (naive MK801: $87.2 \pm 5.0\%$, $n = 8$; pseudo-trained: $106.9 \pm 8.1\%$, $n = 8$; trained: $93.9 \pm 9.3\%$, $n = 8$, one-way ANOVA $F_{(5,40)} = 0.522$, $P > 0.05$; Fig. 2A). In contrast, we see a significant decrease in the level of NR2b in subjects trained in the absence of MK801 (% of naive saline controls: pseudo-trained: $89.9 \pm 14.4\%$, $n = 7$; trained: $77.5 \pm 7.0\%$, $n = 8$; naive MK801: $98.3 \pm 7.4\%$, $n = 8$; pseudo-trained MK801: $89.9 \pm 8.0\%$, $n = 8$; trained MK801: $87.1 \pm 5.0\%$, $n = 8$, one-way ANOVA $F_{(5,40)} = 13.687$, $P < 0.01$, $*P < 0.02$ vs. naive saline controls; Fig.

2B). This suggests that the significant increase observed in NR2a/NR2b following OD learning is due to the decrease in NR2b, rather than an increase in NR2a.

We have previously shown that OD learning is accompanied by a change in NMDAR subunit composition but no change in the level or composition of the AMPA subtype of glutamate receptor (Quinlan et al. 2004). To investigate whether changes in AMPA receptor levels can be detected following OD learning in the presence of MK801 we performed quantitative immunoblotting for AMPAR subunit proteins. We began by quantifying the level of GluR2, as the majority of AMPARs in the adult mammalian cortex contain this subunit (Hollmann et al. 1991). We see no differences in the level of GluR2 subunit of AMPARs in synaptoneurosomes prepared from naive, pseudo-trained, or trained animals injected with MK801 (% of naive saline controls: naive MK801: $102.6 \pm 10.6\%$, $n = 8$; pseudo-trained MK801: $98.8 \pm 8.2\%$, $n = 8$; MK801-trained: $108.6 \pm 14.8\%$ of naive saline controls, $n = 8$; one-way ANOVA $F_{(3,29)} = 0.172$, $P > 0.05$; Fig.

Figure 2. Olfactory discrimination (OD) learning induces a decrease in the level of the NR2b subunit of the NMDAR. (A) OD learning does not regulate levels of the NMDAR subunit protein NR2a. We see no change in the levels of NR2a when OD learning is achieved in the presence or absence of MK801 (one-way ANOVA, $F_{(5,40)} = 0.522$, $P > 0.05$). (Inset) Representative immunoblots for the NR2a subunit of the NMDAR from synaptoneurosomes prepared from the piriform cortex in each experimental condition. Values are normalized to the average naive saline run on the same gel. (B) Learning in the absence of MK801 (saline-treated controls) is accompanied by a decrease in NR2b. When OD learning is achieved in the presence of pre-training injections of MK801, we see no change in the level NR2b (one-way ANOVA, $F_{(5,40)} = 13.687$, $P < 0.01$, $*P < 0.02$ vs. naive-saline controls). (Inset) Representative immunoblots for the NR2b subunit of the NMDAR from synaptoneurosomes prepared from the piriform cortex in each experimental condition. Values are normalized to the average naive saline run on the same gel.

3, left). Similarly, we see no differences in the level of GluR1 in synaptoneurosomes prepared from naive, pseudo-trained, or trained animals injected with MK801 (% of naive saline controls: naive MK801: $83.8 \pm 5.7\%$, $n = 8$; pseudo-trained MK801: $90.9 \pm 5.4\%$, $n = 8$; MK801-trained: $101.2 \pm 4.6\%$, $n = 8$; one-way ANOVA $F_{(3,29)} = 2.006$, $P > 0.05$, Fig. 3, right).

Discussion

Learning a complex task, such as finding the hidden platform in a Morris water maze, can occur in the presence of NMDAR antagonists, particularly if the subjects are pre-trained in the general requirements of the task (Bannerman et al. 1995; Saucier and Cain 1995). Here we show that subjects are capable of acquiring the skill needed to perform an OD task in the presence of an NMDAR open channel blocker even without pre-training. Whereas a gradual improvement in performance becomes evident in control subjects after four days of training, MK801-treated subjects show little improvement until day 9 of training. This suggests that there may be a temporal constraint in the development of alternative, NMDAR-independent learning strategies (Hoh et al. 1999). In addition, the observation that MK801 delays, but does not inhibit, olfactory discrimination learning suggests that the MK801 does not inhibit motivation or sensorimotor capabilities.

In many systems, learning-induced enhancement of synaptic strength occludes NMDAR-dependent long-term potentiation (LTP) suggesting a common mechanism (Riout-Pedotti et al. 2000; Brun et al. 2001; Quinlan et al. 2004). This suggests that in the absence of pharmacological or other constraints, there may be a preference toward NMDAR-dependent synaptic strengthening (Schroeder and Schinnick-Gallagher 2004). However, the presence of NMDAR antagonists may require subjects to employ alternative, NMDAR-independent strategies. For example, to learn the Morris water maze in the presence of NMDAR antagonists, subjects may switch from an NMDAR-dependent spatial strategy to an NMDAR-independent heading vector strategy (Pearce et al. 1998). The intracellular signaling cascades that support the switch from NMDAR-dependent to NMDAR-independent synaptic plasticity are unknown but are likely to include differential regulation of intracellular calcium dynamics. For example, transgenic knock-out of ryanodine receptors specifically facilitates NMDAR-independent, but not NMDAR-dependent, LTP (Futatsugi et al. 1999). In addition, when learning occurs in the presence of MK801, there is a switch to the expression of a difference subset of plasticity-related late response genes (Kesslak et al. 2003; Thompson et al. 2003), consistent with the idea that both NMDAR-dependent and NMDAR-independent synaptic plasticity require transcription for long-term maintenance.

Different stimulation protocols may preferentially elicit NMDAR-dependent versus NMDAR-independent LTP. When LTP is induced in the lateral amygdala in vitro by tetanic stimulation that produces prolonged postsynaptic depolarization, LTP is dependent on NMDARs but not on voltage-gated calcium channels. However, when LTP is induced by pairing weak presynaptic stimulation with strong postsynaptic depolarization, LTP is dependent on the activation of voltage-gated calcium channels, but not NMDARs (Bauer et al. 2002). Interestingly, NMDAR-dependent and NMDAR-independent LTP can also coexist at different synapses with the same postsynaptic target (Fu and Schinnick-Gallagher 2005).

NMDAR function has recently been shown to be down-regulated in the lateral amygdala following fear conditioning (Zinebi et al. 2003) and in the piriform cortex by olfactory discrimination learning (Quinlan et al. 2004). Here we show that the learning-induced increase in the NR2a/NR2b observed in the adult cortex is due to a decrease in the level of the NR2b. Interestingly, it has recently been demonstrated that during a critical period in early postnatal development, sensory experience induces an increase in the ratio of AMPA to NMDA-mediated EPSCs in the lateral olfactory tract, because of a decrease in the contribution of NMDARs (Franks and Isaacson 2005). In contrast, there is no developmental change in the contribution of AMPA relative to NMDA-mediated currents in the intrinsic connections in the

Figure 3. No change in the level of the GluR1 or GluR2 subunit of the AMPAR when olfactory discrimination (OD) learning occurs in the presence of MK801. In the absence of MK801, there is no significant difference in GluR1 (one-way ANOVA, $F_{(3,29)} = 0.172$, $P > 0.05$) or GluR2 (one-way ANOVA, $F_{(3,29)} = 2.006$, $P > 0.05$) in synaptoneurosomes prepared from piriform cortex of trained vs. pseudo-trained and naive controls. (Inset) Representative immunoblots for GluR1 and GluR2 of synaptoneurosomes prepared from the piriform cortex in each experimental condition. Values are normalized to the average naive saline run on the same gel.

piriform cortex. Differential regulation of NMDAR during development may underlie the differences in NMDAR-dependent synaptic plasticity in these two classes of synapses (Jung et al. 1990; Kanter and Haberly 1993).

We have previously proposed that NMDAR subunit switching induced by learning would constrain subsequent NMDAR-dependent synaptic plasticity and preserve the memory encoded by experience (Quinlan et al. 2004). However, here we show that learning persists in the presence of MK801 and the absence of NMDAR subunit switching. Interestingly, subjects that learned to navigate the Morris water maze in the presence of MK801 showed reduced success on a post-training probe trial, suggesting that MK801 disrupted the duration of the memory (Guscott et al. 2003). It remains to be seen if memory duration is less stable if OD learning occurs in the absence of NMDAR subunit switching.

Materials and Methods

Subjects and apparatus

Adult, male Sprague-Dawley rats were maintained on a 23.5-h water-deprivation schedule, with food available ad libitum, for 3 d before the beginning of training. As in previous studies (Saar et al. 1998, 1999; Quinlan et al. 2004), water-deprived subjects did not show signs of stress, such as weight loss, and performed well in the OD task. All animal care and use conformed to NIH guidelines with the approval of Haifa University and the University of Maryland Animal Care and Use Committees.

Training

Trained and pseudo-trained subjects were given daily OD training in a four-arm radial maze, with commercially available odors from the cosmetics and food industries. At the beginning of each session, an electronic signal randomly opens two valves, releasing a positive-cue odor into one arm and a negative-cue odor into the other. After eight seconds, the electronic doors controlling access to these two arms are opened, and the subject must choose an arm to enter. When the subject reaches the end of an arm, an infrared beam is interrupted. During training, if the animal enters the arm containing the positive-cue odor, a drop of drinking water is released into the well at the end of that arm. The association between water reward and odor is random for pseudo-trained controls. The trial ends when the infrared beam is interrupted, or 10 sec after the doors are opened. OD training consisted of 20 trials per day. The criterion for learning was set at $\geq 80\%$ positive-cue choices for the last 10 trials of the day. The pseudo-trained group of age-matched controls was exposed to the same number of training trials, but with a random associa-

tion between odor and reward. An age-matched group of naive controls was water deprived, but not exposed to odors, rewards, or the maze. Once criterion for learning to discriminate between the first pair of odors was reached by all the subjects in the trained group, the next day both trained and pseudo-trained groups began training with the next pair of odors.

Drug application

The NMDAR open channel blocker dizocilpine (MK801) or vehicle (sterile saline) was injected intraperitoneally (0.1 mg/kg) 2 h before each training session (Keseberg and Schmidt 1995; Pitkanen et al. 1995). The trainer was blind to experimental condition.

Quantitative immunoblotting

Equal amounts of synaptoneurosomes protein (prepared as described, Heynen et al. 2000; Quinlan et al. 2004), determined using the BCA assay (Pierce), were resolved on 8% polyacrylamide gels, transferred to nitrocellulose and probed with either anti-NR2A or anti-NR2B (both 1:1000; polyclonal, Upstate Biotechnology), anti-NR1 (1:1000, monoclonal 54.1 Pharmingen), anti-GluR1 (1:500; polyclonal, Upstate Biotechnology), anti-GluR2 (1:500; polyclonal, Chemicon) or anti-actin (1:1000; monoclonal JLA20, Oncogene) antibodies, followed by the appropriate secondary antibody coupled to horseradish peroxidase (1:3500, Sigma Immunochemicals) in Tris buffered saline at pH 7.3 containing 1% bovine serum albumin and 0.1% Triton-X 100 (Sigma). Visualization of immunoreactive bands was produced by enhanced chemiluminescence (Amersham ECL) captured on autoradiography film (Amersham Hyper ECL). Digital images, produced by densitometric scans of autoradiographs on a ScanJet IIcx (Hewlett Packard) with DeskScan II software (Hewlett Packard), were quantified using NIH Image 1.60 software. The optical density of each band was determined relative to a baseline immediately above and below the band within the same lane, and normalized to the optical density of actin as a gel-loading control. Data are normalized to the average of 2–3 naive saline controls run on the same gel.

Statistical analysis

Group data are the mean $\pm$ SEM of the normalized optical density. Statistical significance was determined using one-way ANOVA with post hoc comparisons. Immunoblotting was performed blind to the experimental condition.

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